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(54) Title: USE OF TAUROLIDINE OR TAURULTAM FOR THE MANUFACTURE OF A MEDICAMENT FOR THE PREVENTION OF METASTASES			
(57) Abstract			
<p>The invention provides the use of taurolidine or taurultam solutions to prevent or reduce metastatic growth. This is of particular application in preventing or reducing the incidence of metastatic growth following surgery, particularly following the use of trocars during minimal invasive laparoscopic surgery.</p>			

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USE OF TAUROLIDINE OR TAURULTAM FOR THE MANUFACTURE OF A MEDICAMENT FOR THE PREVENTION OF METASTASES

5 This invention relates to a method for preventing metastases, in particular to a method for preventing metastatic growth of malignant tumours. More particularly it relates to a method for preventing metastatic growth following surgery, and especially
10 minimally invasive abdominal surgery, such as endoscopic, e.g. laparoscopic, surgery.

Malignant tumours within the body, and particularly the abdomen are frequently removed surgically. The exploration and excision of tumours by major invasive
15 surgery has been used for many years but, more recently, minimal invasive surgery has increasingly been used.

A wide range of indications of malignant tumours exist for which invasive surgery, such as laparotomy or laparoscopy, may be used. These include, but are not
20 restricted to, the following: oesophagus carcinoma (plaster cell carcinoma, adenocarcinoma) and cardiac carcinoma; malignant degenerative ulcer; carcinoma of the stomach, antrum or corpus, malign adenoma of island cells, re-section or total gastrectomy; carcinoma of the gall duct or distal choledochus; carcinoma of the pancreas head, papilla, corpus or cauda; carcinoma of the small or large intestinal tract, sarcoma; colon malignancy: adeno carcinoma, lymphoma, malign carcinoid, melanoma, fibrosarcoma; carcinoma of the rectum; ovarian carcinoma; mamma carcinoma; and prostate carcinoma.
30

The use of minimal invasive surgery has brought with it a reduced mortality and a reduced post-operative infection rate. Classic open abdominal surgery, or laparotomy, for example, may require less operation time
35 than minimal invasive surgery, but involves long post-operative convalescence and a greater risk of infection, e.g. sepsis. One reason why minimal invasive

- 2 -

laparoscopies are on the increase is the drastically reduced amount of time that the patient needs to spend recuperating both in hospital and at home. Laparoscopy also has the advantage that there is a significant
5 reduction in wound scars and in post-operative complications associated with wound healing.

A wide range of laparoscopic procedures are in general use, including laparoscopic cholecystectomy, laparoscopic fundoplication (anti-reflex surgery for
10 gastro-oesophageal disease), laparoscopic treatment of para-oesophageal hernia, laparoscopic treatment of abdominal cysts (e.g. liver cysts removed by cystectomy), laparoscopic liver re-section, laparoscopic appendectomy, laparoscopic treatment of intestinal
15 obstruction (e.g. incarcerated hernias, colon obstruction and massively dilated small bowel obstruction), laparoscopic colo-rectal surgery (e.g. ileosacral re-section, hemicolectomy, sigma-resection, rectum prolapse and rectum amputation), laparoscopic adhesiolysis, emergency laparoscopy (exploratory diagnosis), differential diagnosis of appendicitis,
20 acute abdomen, ileus, abdominal trauma, and oncological queries (e.g. to determine whether or not carcinoma is operable).

25 One aspect of minimally invasive laparoscopies which gives rise to concern, particularly when these are used to combat abdominal malignancies, is the extent to which metastatic growth has been observed. It is now recognised that manipulation of a malignancy can result
30 in a disturbance and release of malignant cells which can then travel to other locations where, if they adhere and start growing, form metastases with predictably unfortunate results. This risk is lower during a classic open laparotomy, for example, so that the whole tumour is carefully excised and removed without
35 transferring any cells to other parts of the abdomen. In a minimally invasive laparoscopy using a trocar,

- 3 -

however, this may not be possible and disturbance of the tumour and its contact with adjacent tissues whilst being removed are inevitable. It has been found that "trocar metastases" are often a result of minimally invasive abdominal surgical procedures, e.g. laparoscopic surgery.

One reason for the frequent observation of metastases following laparoscopic intervention is believed to reside in the use of the trocar tubes or sleeves, the diameters of which may range from 5 to 20 mm. These can either result in damage to malignant tissues or may otherwise come into contact with cell-rich exudate which then drips from the trocar sleeve into the abdominal cavity thereby initiating metastases.

To effect the removal of re-sected organs or pieces from the abdomen, a "rescue" bag is introduced via the trocar sleeve. This is particularly so when removing inflamed re-sections or neoplastic tissue in an attempt to prevent contamination of the abdominal cavity by resected neoplastic cells or cell threads of the primary tumour.

We have now found that the incidence of metastases following surgery, and in particular trocar metastases believed to be caused by laparoscopic operations, can be reduced if the area affected during the operation and any other internal tissue or organ with which any of the apparatus or tumour comes into contact is instilled with a solution containing taurultam, taurolidine or a mixture thereof.

In studies that have been carried out on animal models, a significant suppression in the growth or spread of tumours following instillation of taurultam or taurolidine has been observed.

Accordingly, viewed from one aspect, we provide the use of taurultam or taurolidine solutions to prevent or reduce metastatic growth. This is of particular application in preventing or reducing the incidence of

- 4 -

metastatic growth following surgery, and particularly following the use of trocars during minimal invasive laparoscopic surgery, but has general application.

Viewed from a further aspect, we provide the use
5 taurolidine and/or taurultam in the manufacture of a medicament for the prevention of metastases, in particular for the prevention or reduction of metastatic growth.

A preferred solution will contain from 0.5 to 3% by
10 weight of taurolidine, or from 2 to 3% by weight taurultam, depending on the solubility of the compound. Solutions containing from 0.5 to 1.0% or 2.0% taurolidine are preferred.

The solutions will generally be made up in sterile
15 pyrogen-free water and may also contain, for example, inorganic or other salts or other components to render them isotonic. Parenterally acceptable polyols may, for example, also be present since these have been observed to increase the overall intravenous tolerance of
20 taurolidine. Suitable polyols include carbohydrates, e.g. hexoses such as glucose and fructose (or mixtures of these such as invert sugar), pentoses such as xylose or polysaccharides such as dextran or hydrolysed starch; glycerol and sugar alcohols such as sorbitol, mannitol
25 or xylitol.

The concentration of the polyol can usefully be in the range 3-40% by weight. In the case of glucose, the concentration may be in the range 10-30% by weight, preferably 20%.

30 The solutions may also contain polyvinylpyrrolidone (PVP). This may be incorporated into the solutions at a concentration of, e.g. from 4 to 7% by weight. A solution containing 5% PVP is preferred. This assists in solubilising the active substance and contributes
35 also to the oncotic pressure of the solution. The molecular weight of the PVP should not be greater than 30,000 and is preferably less than 10,000, for example

- 5 -

between 7000 and 9000. Kollidone 17 as sold by BASF is relatively quickly resorbed and excreted renally.

The exact mode of action of taurolidine or taurultam in preventing metastatic growth under these circumstances is still not known. Without wishing to be bound by theoretical considerations, we believe that the taurolidine or taurultam is capable of altering the protein structure surface of the adhesion molecules (receptors) such as I-P-selectine and fibronectine. It is believed that over-expression of molecules such as these, and including also integrine, vitronectine and laminin, are the principal cause of metastatic development since they are believed to provide the malignant cells with the ability to migrate and adhere to other cell surfaces and endothelium, in particular to vascular endothels. The malignant cells then become sedentary, allowing themselves to grow and further develop (metastases). Once developed, such cells are able to reach every organ either through the haematogenic or lymphatic channels (formation of metastases).

It is believed that the taurolidine or taurultam modifies the surface structure of the malignant cell in such a way that over-expression of the adhesion molecules is reduced. As a result, adhesion of the malignant cells to other cell surfaces and endothelium, e.g. to endothels, is reduced or does not occur before the cell itself dies. The active agent is not believed to have any direct cytotoxic effect on the malignant cells. Taurolidine or taurultam is also believed to prevent high cytokine levels, e.g. IL-1 β , in peritoneal fluid, which in turn prevents tumor cell proliferation and adhesions. The taurolidine or taurultam is thus being used essentially prophylactically.

The taurolidine or taurultam solution may be used simply by instillation, as an aerosol (a nebulised solution of taurolidine or taurultam) and/or by

- 6 -

intravenous infusion. When being used in conjunction with a surgical procedure, it may be administered either prior to, during or after the surgical procedure being carried out. If used as an instillation to irrigate the 5 surgically affected area, it will be administered intra-operatively or before closure of the surgical incision. In minimal invasive surgery, the solution can be passed through the trocar tubes or sleeves.

In general, in preparation for laparoscopy the 10 abdominal wall is lifted. This may be achieved either by insufflation (pneumoperitoneum) or mechanically. Special instruments are required to raise the abdominal wall without causing damage to the intestinal loops. A Veres needle having an opening on one side through which 15 a gas may enter the abdominal cavity is generally used for preparation of the pneumoperitoneum. Gases conventionally used for insufflation include N₂O, CO₂ and helium which may be introduced into the abdominal cavity at a rate of up to 1 litre/min. Depending on the 20 patient's body size and tissue tension, between 3 and 5 litres of CO₂ gas may be required. For diagnostic laparoscopy under local anaesthetic, N₂O is preferred since, unlike CO₂, this does not irritate the peritoneum. Whilst not wishing to be bound by theory, it is believed 25 that this irritation could be one of the reasons for the more frequent appearance of metastases observed when using CO₂.

A metal suspension bar is conveniently used to lift the abdominal wall mechanically. Once inserted into the 30 abdomen, special hooks are attached to the suspension bar and the abdomen is then raised using a chain and suspension scale.

According to the type of surgical procedure, for example in minimally invasive abdominal surgery, from 35 100-1000 ml, preferably from 100-250 ml, of a 2%, 1% or 0.5% taurolidine solution can be instilled at body temperature and allowed to remain in the abdominal

- 7 -

cavity after the end of the operative procedure, and before extraction of the gas used in the pneumoperitoneum (which enlarges the abdominal cavity and with which the laparoscopy starts) and final removal 5 of the trocar.

For the prophylaxis of post-operative complications, particularly trocar metastases, a 2% Taurolin, a 0.5% Taurolin-Ringer or a 2-3% taurultam solution may be used. Conveniently, the abdomen is 10 rinsed with such a solution using a rinse-suction tube. A 5 or 10 litre rinse bag is filled with the desired rinse solution (isotonic saline or ringer solution) and hung at a height of approx. 2 m. 1-2 litres of rinse solution are then introduced through the rinse-suction 15 tube. Following a short contact time (sufficient to ensure that the intestinal loops are completely covered by the rinse solution) the solution is then suctioned off. In cases of severe inflammation, the rinsing solution will appear opaque such that abdominal visibility using the optic and camera is poor. In such 20 cases, this rinsing procedure must be repeated until the liquid in the abdomen is clear and translucent.

When the rinsing procedure is complete and the solution is clear, the rinse bag is then filled with 250 ml 2% Taurolin (pre-warmed to 37°C) which is allowed to flow into the abdominal cavity. Finally, a drain is inserted before closure of the abdomen. In severe cases, e.g. severe peritonitis, it is possible to instill (and in some cases to leave) up to 1000 ml 25 Taurolin 2% solution within the abdominal cavity. In place of a 2% Taurolin solution, 1-1.5 litres Taurolin-Ringer 0.5% solution or a 2-3% taurultam solution may be used.

In patients with malignant tumours it is 35 particularly advantageous to additionally administer Taurolin 2% intravenously through a central catheter as a drop infusion, e.g. at a dosage of 4 x 250 ml per

day). If necessary, the drop infusion may be continued for 2 - 3 days following surgery.

Alternatively, the 2% Taurolin solution may be instilled and suctioned off using a pressure-rinse apparatus. Another variation is to attach a pressure-cuff to the rinse bag whereby suction may be carried out using a suction-off apparatus. It is also possible to use an infusion pump as an alternative to instillation.

In a preferred embodiment of the invention, the taurolidine or taurultam solution will be used simultaneously with heparin. The use of heparin alone has not been found significantly to influence metastatic growth but the use of heparin in conjunction with taurolidine, administered either in combination or separately, has been found to give a significant, synergistic effect. The desired dosage of heparin depends on the result of the blood coagulation test. Thus, this will vary from patient to patient but can nevertheless be readily determined by those skilled in the art. An average dosage of heparin can be expected to be in the range of from 230 to 625 I.U. heparin-Na/kg bodyweight. In general, 5000 I.U. heparin-Na might be administered up to 2 hours prior to surgery.

For use in laparoscopic surgery, standard-heparin-sodium or standard-heparin-calcium may be added to the taurolidine solution immediately prior to application. Alternatively, low molecular weight heparin may be used. Typically, 200-500 ml 0.5-1.0% Taurolin in isotonic saline or Ringer-solution may be administered in combination with 1000-5000 I.U. heparin via a trocar tube.

The taurolidine-heparin solution may conveniently be applied under pressure, e.g. approx. 10-12 mm Hg, by means of a micro-pump. Administered in this way, the solution enters the abdominal cavity as an aerosol, resulting in a more widespread application of the solution to all exposed interabdominal (interior and

- 9 -

lateral) surfaces during surgery. Administration of the solution as an aerosol also results in an increased efficacy during pneumoperitoneum with carbon dioxide.

In an alternative embodiment of the invention, the
5 taurolidine or taurultam solution may be used simultaneously with hyaluronic acid, e.g. with a 0.1% hyaluronic acid sodium salts pharmaceutical grade solution, preferably having a molecular weight of 2.5×10^6 Da.

10

Test Procedure

To prevent intraperitoneal tumour growth and trocar metastases caused by laparoscopic operations, the effect of taurolidine and heparin were investigated on the
15 growth of colon carcinoma cells (DHD/L12/TRb) in vitro, as well as in rat models. After incubation of the cells with heparin, taurolidine or both substances there followed the in vitro determination of the growth kinetics of the cells. A second experiment followed on
20 rats ($n=60$) following intraperitoneal application of tumour cells and subsequently the development of a pneumoperitoneum for 30 mins. The rats were randomised into 4 groups:

25

- I Tumour cells
- II Tumour cells + heparin
- III Tumour cells + taurolidine
- IV Tumour cells + taurolidine + heparin

30

Results

Where the tumour growth in vitro was not affected by heparin, a significant suppression of growth was observed with taurolidine and taurolidine/heparin. In vivo, however, the intraperitoneal tumour weight
35 compared to the control group (596 ± 278 mg) was reduced both with the instillation of heparin (298 ± 155 mg) as well as with taurolidine (149 ± 247 mg). The

- 10 -

combination of both substances caused a further average tumour weight reduction of (21.5 ± 36 mg). The development of trocar metastases could be significantly suppressed using either taurolidine alone, or the 5 combination of taurolidine and heparin.

The following non-limiting examples serve to further illustrate the invention.

Example 1 - laparoscopic procedure

10

In a typical abdominal procedure, which should not be considered as limiting, a 0.5% taurolidine Ringer solution at body temperature is rinsed through the suction rinse tube under minimal pressure intra-operatively.

15 According to the extent of surgical invasion, from 100-250 ml 2% taurolidine is instilled at 37°C and allowed to remain in the abdominal cavity on conclusion of the operative procedure.

20

Example 2 - laparoscopic procedure

25

A typical abdominal procedure may be carried out in accordance with Example 1, except that the 2% taurolidine solution is replaced by a 500 ml 0.5% taurolidine Ringer solution used in combination with 2500 I.U. heparin. This solution is instilled into the abdominal cavity via drains which are then clamped for 2 hours.

30

Example 3 - laparotomy (partial pancreatectomy)

35 In a typical treatment of pancreas head carcinoma, the operation site is meticulously rinsed with approx. 500-1000 ml warm (37°C) 0.5% Taurolin-Ringer solution. After 10 minutes contact time, the solution is suctioned off.

- 11 -

Every 20 minutes the operation site is moistened with 100-200 ml 2% Taurolin solution using a large calibrated curved syringe.

5 After 10-15 minutes contact time the solution is suctioned off. Before final closure of the abdominal wall, 250 ml Taurolin 2% solution* (with heparin added according to the blood coagulation results) is instilled.

10 * Alternatively, 2-3% taurultam may be used.

Example 4 - laparotomy (radical mastectomy)

15 In a typical treatment of mamma carcinoma (radical mastectomy), the operation site is rinsed intraoperatively every 20 minutes using 200 ml Taurolin 2% solution. If possible, a 10 minute contact time is permitted by lifting the surgical drapes thereby preventing the rinse solution from draining away too 20 quickly.

The operation wound is then closed and drained.

25 Additionally, intraoperative per drop infusion of 250 ml 2% Taurolin solution is administered via a central catheter (dosage: 4 x 250 ml per 24 hours).

Example 5 - laparoscopic procedure

30 In a typical abdominal procedure, a taurolidine solution is administered in the form of an aerosol. This may be achieved through the use of a micro-pump which is situated between a gas (e.g. CO₂) supply and the abdominal cavity in which surgery is to be performed. A tube is used to carry the aerosol into the trocar tube or sleeve. The taurolidine solution may be administered 35 continuously as a spray during abdominal surgery, e.g. at a rate of 100 to 200 ml per hour.

- 12 -

Claims:

1. Use of a solution comprising taurolidine, taurultam or a mixture thereof in the manufacture of a medicament
5 for use in a method of preventing or reducing metastatic growth.
2. Use as claimed in claim 1 for preventing or
reducing metastatic growth following surgery.
10
3. Use as claimed in claim 2 for preventing or
reducing metastatic growth following minimal invasive
surgery.
15
4. Use as claimed in claim 2 or claim 3 for preventing
or reducing metastatic growth following the use of
trocars during laparoscopic surgery.
20
5. Use as claimed in any one of claims 1 to 4 wherein
the solution contains from 0.5 to 3% by weight of
taurolidine or from 2 to 3% by weight of taurultam.
25
6. Use as claimed in any preceding claim wherein said
method comprises administering said medicament
separately or sequentially with heparin, a heparin
derivative or hyaluronic acid.
30
7. Use of (i) a solution comprising taurolidine,
taurultam or a mixture thereof, and (ii) heparin, a
heparin derivative or hyaluronic acid, for the
manufacture of medicaments for separate or sequential
administration in a method of preventing or reducing
metastatic growth.
35
8. A pack containing a solution comprising
taurolidine, taurultam or a mixture thereof, and
separately heparin, a heparin derivative or hyaluronic

- 13 -

acid for simultaneous, separate or sequential use in a method of preventing or reducing metastatic growth.

9. A method of preventing or reducing metastatic
5 growth in a human or non-human mammalian body, said
method comprising administering to said body an
effective dose of a solution comprising taurolidine,
taurultam or a mixture thereof.
10. A method as claimed in claim 9 for preventing or
reducing metastatic growth following a surgical
procedure in which said solution is administered prior
to, during or after the surgical procedure.
15. A method as claimed in claim 9 or claim 10 wherein
said solution is administered by instillation or
intravenous infusion.
20. A method as claimed in claim 9 or claim 10 wherein
said solution is administered in the form of an aerosol
using a micro-pump.
25. A method as claimed in any one of claims 9 to 12
further comprising administering to said body separately
or simultaneously heparin, a heparin derivative or
hyaluronic acid.
30. A pharmaceutical composition for use in preventing
or reducing metastatic growth comprising taurolidine
and/or taurultam, together with heparin, a heparin
derivative or hyaluronic acid.

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INTERNATIONAL SEARCH REPORT

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PCT/GB 98/02311

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/54 A61K31/715

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	C.A.JACOBI ET AL.: "Peritoneale instillation von Taurolidin und Heparin zur Verhinderung von intraperitonealem Tumorwachstum und Trokarmetastasen bei laparoskopischen Operationen im Rattenmodell" LANGENBECKS ARCH CHIR, vol. 382, no. 4 suppl 1, 25 July 1997, pages S31-S36, XP002083832 see abstract ---	1-5,9-12
X	WO 92 00743 A (ED GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE) 23 January 1992 see page 1 see page 2, paragraph 4 see page 3, paragraph 3 ---	1-5,9-12
Y		6-8,13, 14 -/-

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DE 196 06 897 A (J.M.MÜLLER ET AL.) 14 August 1997 see abstract ---	1-5,9-12
X	WO 95 18638 A (ED GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE) 13 July 1995 see claims 1,10,14 ---	14
Y	DATABASE WPI Section Ch, Week 8607 Derwent Publications Ltd., London, GB; Class A96, AN 86-045778 XP002091627 & JP 61 000017 A (SEIKAGAKU KOGYO CO LTD) , 6 January 1986 see abstract ---	6-8,13, 14
Y	WO 95 30423 A (NORPHARMCO INC.) 16 November 1995 see abstract -----	6-8,13, 14

INTERNATIONAL SEARCH REPORT

international application No.
PCT/GB 98/02311

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-14 (6-8,13,14 only partly in so far as hyaluronic acid is concerned)

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-5,9-12

Use of taurolidine or taurultam for preventing and treating metastatic growth

2. Claims: 6-8 and 13-

14 each partly in so far as the combination with heparin and derivatives is concerned

Use of taurultam or taurolidine in combination with heparin or a derivative thereof and compositions containing these agents

3. Claims: 6-8 and 13-

14 each partly in so far as the combination with hyaluronic acid is concerned

Use of taurultam or taurolidine in combination with hyaluronic acid and compositions containing these agents

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/02311

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 9200743	A	23-01-1992		EP 0491018 A JP 5500973 T		24-06-1992 25-02-1993
DE 19606897	A	14-08-1997		NONE		
WO 9518638	A	13-07-1995		CA 2180659 A EP 0738161 A JP 9507144 T US 5837278 A		13-07-1995 23-10-1996 22-07-1997 17-11-1998
WO 9530423	A	16-11-1995		CA 2122519 A AU 696373 B AU 2402395 A CN 1151118 A CZ 9603089 A EP 0760667 A HU 75868 A JP 9512797 T WO 9407505 A WO 9526193 A WO 9529683 A WO 9606622 A WO 9817320 A US 5792753 A US 5834444 A US 5614506 A US 5827834 A US 5852002 A US 5830882 A US 5817642 A US 5811410 A US 5817644 A		30-10-1995 10-09-1998 29-11-1995 04-06-1997 14-01-1998 12-03-1997 28-05-1997 22-12-1997 14-04-1994 05-10-1995 09-11-1995 07-03-1996 30-04-1998 11-08-1998 10-11-1998 25-03-1997 27-10-1998 22-12-1998 03-11-1998 06-10-1998 22-09-1998 06-10-1998